L-02-0017
Study 3

Acute Oral Toxicity Study in Rats (980431); October 16, 1998

REDACTED AS TO TRADE NAMES

LABORATORIES & CLINICS GROUP
BIOSCIENCE

RBM Via Ribes 1
10010 Colleretto Giacosa (TO)
Italy

Tel: 0125 222111
Fax: 0125 222599

[redacted]

[redacted] $Ce(C_3F_6O)_3\text{-}CF_2COO^-NH_4^+$

"ACUTE ORAL TOXICITY STUDY IN RATS"

RBM EXP. No. 980431

EEC Guidelines (B.1)
OECD Guidelines (401)

Issued on October 16, 1998

SPONSOR

AUSIMONT
Viale S.Pietro, 50/A
20021 BOLLATE (Milano)
Italy

PERFORMING LABORATORY

Istituto di Ricerche Biomediche
"Antoine Marxer" RBM S.p.A.
Via Ribes, 1
10010 - COLLERETTO GIACOSA (Torino)
Italy

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RBM Exp. No. 980431

TITLE OF THE STUDY

"Acute oral toxicity study in rats treated with the test article [redacted] "

PURPOSE OF THE STUDY

The purpose of the study was to evaluate the acute oral toxicity of the test article [redacted].

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RBM Exp. No. 980431

FOREWORD

On behalf of **AUSIMONT Viale S.pietro, 50/A. 20021-BOLLATE-Milano-Italy**, Istituto di Ricerche Biomediche "Antoine Marxer" RBM S.p.A., authorized by the Italian Health Authorities (1-2) to conduct safety studies, has performed an acute toxicity study by oral route in Sprague Dawley Crl: CD(SD) BR rats (RBM-Experiment No. 980431), with the test article:

[redacted]

A sample of the substance used, along with pertinent documentation, is held in sufficient quantity in the RBM archives and is at the disposal of the Ministero della Sanità.

The undersigned declares that the experiment was conducted using the same batch of substance as that of the sample held on file.

For verification by the Ministero della Sanità, the undersigned moreover guarantees the identification and classification of all those materials, documents and recordings used in conducting the experiment, held on file for a period of at least 10 years from the date of this report. Following this time, they will be placed at the disposal of the Sponsor.

Dr. Roberto Maraschin
Scientific and Operative Director

Ivrea, October 16, 1998

(1): **Pharmaceuticals:**
Authorization dated March 12, 1976 in accordance with "Circolare 73", May 16, 1974

(2): **Chemicals:**
Authorization in accordance with DPR 927/81 (D.M. dated January 7, 1988 published in G.U. No. 12, dated January 16, 1988).

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RBM Exp. No. 980431

QUALITY ASSURANCE STATEMENT

RBM Experiment number: 980431

Study title:

"Acute oral toxicity study in rats treated with the test article [redacted]"

Studies of the type described in this report are conducted in a manner which involves frequent repetition of identical or similar procedures.

In compliance with the Principles of Good Laboratory Practice, at the time of this study, procedure-based inspections were made by the Q.A.U. of critical phases and procedures relevant to this type of study. For the inspection of any given procedure, studies were selected at random. All such inspections were reported promptly to the study director and to facility management.

This study was inspected on:

Dates of inspection/audit	Dates of report to Study Director and Management
May 29, 1998 October 15 – 16, 1998	May 29, 1998 October 16, 1998

This report has been audited by the Q.A.U. and was found to be an accurate description of such methods and procedures as were used during the conduct of the study and an accurate reflection of the raw data.

Date of final report audit: October 20, 1998

Enrico Invernizzi
Head of Quality Assurance Unit

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CERTIFICATION OF GLP COMPLIANCE

Study No. 980431 entitled :

"Acute oral toxicity study in rats treated with the test article [redacted] "

I hereby confirm that this study was conducted in accordance with the OECD [C(81) 30 (final)], Principles of Good Laboratory Practice (GLP).

The Sponsor is responsible for GLP compliance of any information supplied.

These principles were adopted by the EEC and incorporated into EEC Directive 88/320, that was legally enforced by the Italian Health Authority [D.M. dated June 26, 1986 as published in G.U. No. 198, dated August 27, 1986 and D.L. January 27, 1992, No. 120 as published in G.U. (Supplement) No. 40, February 18, 1992].

The final report fully and accurately reflects the raw data generated during the conduct of the study.

This report consists of 42 pages.

Study Director

Dr. Ping Yu

Ivrea, October 21, 1998

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SCIENTISTS INVOLVED IN THE STUDY

Study No. 980431

"Acute oral toxicity study in rats treated with the test article [redacted]"

Study Director	Dr. Ping Yu
Senior Scientist for General Toxicology	Dr. Sergio Peano
Head of General Toxicology I Unit	Dr. Germano Oberto
Centralized Pharmacy Head	Dr. Rita Bussi
Pharmacy Service Head	Dr. Bruna Piccioli

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MATERIALS AND METHODS

EXPERIMENTAL DESIGN

RBM Experiment No.: 980431

Test article: [redacted]

Administration route: oral (by gavage)

Duration of treatment period: single administration

Duration of post-treatment observation period: 14 days

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.1) and with Organization for Economic Cooperation and Development Guidelines (section 4, subpart 401, Paris 1981 and subsequent revisions).

TEST SYSTEM

Species, strain and substrain: Sprague Dawley Crl: CD (SD) BR rat

Justification for selection of the test system : the Sprague Dawley rat was chosen as rodent species since it is an appropriate experimental model widely accepted by Health Authorities, with documented susceptibility to a wide range of toxic substances

Number and sex of animals: 5 males/dose at the doses of 63, 81 and 145 mg/kg
5 males and 5 females at the dose of 45 mg/kg.

Supplier:	Charles River Italia S.p.A. Via Indipendenza, 11 22050 CALCO (Lecco) Shipping slips Nos. 03930 (May 29, 1998), 04317 (June 12, 1998), 04479 (June 19, 1998), 04635 (June 26, 1998) and 05128 (July 17, 1998)
Age (at randomization):	no more than three months
Body weight (at randomization):	Males: 242-302 g Females: 207-230 g
Acclimatization:	at least 5 days before the start of the test. Animals were observed daily to ascertain their fitness for the study.
Housing:	5 animals/sex/cage in air-conditioned room. - Temperature: 22°C ± 2 - Relative humidity: 55% ± 10 - Air changes: about 20 / hour filtered on HEPA 99.97% - Light: 12 hour cycle (7 a.m. - 7 p.m.) - Cage size: grill cages 40.5x38.5x18h cm with stainless steel feeder. The waste that dropped through the grill bottom onto removable paper was periodically disposed of.
Animal identification:	by appropriately coloring different areas of the limbs. Cage card gave experiment number, dosage group, sex and date of administration.
Diet:	GLP 4RF21 top certificate pelleted diet produced by Charles River Italia's feed licencee Mucedola S.r.l., Settimo Milanese. The declared contents on the label, on dry matter basis (moisture 12%), were:

crude protein	18.50%
crude fat	3.00%
crude fiber	6.00%
crude ash	7.00%

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The diet was supplemented by the Producer with vitamins and trace elements. The Producer supplies a certificate of analysis for nutrients and contaminants, the levels of which are within the limits proposed by EPA-TSCA (44FR:44053-44093, July 26, 1979).
RBM has the animal feed re-analyzed at least twice a year for bacterial contamination.
The diet was available "ad libitum" to the animals.

Water: from the municipal water main system.
Water is filtered and distributed "ad libitum" to the animals by an automatic valve system.
Periodically drinking water is analyzed for microbial count, heavy metals, other contaminants (e.g. solvents, pesticides) and other chemical and physicals characteristics. The accepted limits of quality of the drinking water were those defined in EEC directive 80/778

Contaminants that might interfere with the objectives of the study were not expected to be present in the diet or drinking water.

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TEST ARTICLE, CHARACTERIZATION

Identification:	[redacted]
Batch:	4/SPINETTA
Characteristics:	white powder
Purity:	> 99%
Manufacturing date:	March 30, 1998
Expiry date:	December 2000
Storage conditions:	at room temperature

VEHICLE CHARACTERIZATION

Deionized water

TEST ARTICLE FORMULATE PREPARATION

When required, an exact amount of test article was weighed in a suitable graduated container and made up to final volume with vehicle to obtain the concentration required.

Magnetic stirring was used to obtain a homogeneous suspension. Formulates were kept magnetically stirred until the end of administration and were administered within one hour of the preparation.

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TEST DESCRIPTION

Administration route: oral (by gavage)

Reason for selection of administration route: possible ingestion by humans

Experimental design:

Dose* Mg/kg	Treated animals	Treatment Date	Final killing
145	5 males	July 9, 1998	Found dead
81	5 males	August 4, 1998	August 25,1998
63	5 males	August 20, 1998	September 10, 1998
45	5 males	July 22, 1998	August 5, 1998
45	5 females	August 4, 1998	August 25, 1998

* The doses were defined on the basis of a preliminary study.

Administration method: The volume of administration was 10 ml/kg defined on the basis of the individual body weight. The administration was done by gavage to rats which had been fasted about 16 hours. Feed was returned to the rats about three hours after the test article administration.

Observation period: 14 or 21 *days after administration

* for males in groups of 63 and 81 mg/kg and for females in group of 45 mg/kg due to the delayed clinical changes.

Observation of clinical signs and mortality: at 30 minutes, 2, 4 and 6 hours on the first day after the administration (day 1) and then twice a day up to termination of the observation period

Body weight: twice pre-trial (at randomization and on day 1 just before administration) and on days 3, 8 and 14. On day 1 the animals were weighed after a 16-hour fasting period. For males in groups of 63 and 81 mg/kg and for females in group of 45 mg/kg body weights were also recorded on day 21.

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Gross pathology:	on animals which died before the end of the study and on animals killed (fasted overnight) by excision of the femoral arteries, after i.p. overdosage anesthesia with 5% sodium pentobarbital, at the end of the observation period
Histology:	portions of abnormál entities found in the necropsied animals were collecred. The tissue samples were fixed and preserved in 10% buffered formalin. Histologic examination was not performed
LD_{50} and its statistical limits:	LD_{50} was calculated by the method of the Probit (Bliss - Finney) - A.P. Rosiello et al., J. Tox. and Env. Health, 3: 797-809, 1977.

RECORD FILING

The protocol, a reserve sample of the batch of the test article used, the raw data bound in a register numbered 980431 /1, the specimens, the final report and all other documents pertinent to the conduct of this study, including records and reports of maintenance, cleaning, calibration and inspection of equipment, analysis of diet and water are filed at RBM premises for ten years from the issue date of this report and then sent to the Sponsor.

PROCEDURAL DETAILS

The study was conducted in accordance with the procedures described in the RBM Standard Operating Procedures (SOP's) collection.

Protection of animals used in the experiment is in accordance with Directive 86/609/EEC, enforced by the Italian D. L. No. 116 of January 27, 1992.

Physical facilities and equipment for accommodation and care of animals are in accordance with the provisions of EEC Council Directive 86/609.

The Institute is fully authorized by Competent Veterinary Health Authorities.

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RESULTS

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CLINICAL OBSERVATIONS

MORTALITY *(TABLE 1)*

The mortality which occurred at the various doses is given below:

Dose (mg/kg)	45	63	81	145
Treated animals	5M+5F	5M	5M	5M
Mortality	0	2M	4M	5M
Total (%)	0%	40%	80%	100%

The deaths occurred 4-9 days after dosing, with the first case observed on day 4 after administration in the 145 mg/kg group.

No deaths occurred in the animals of either sex in the lowest dose group (45 mg/kg).

The LD_{50} was calculated to be 67.7 mg/kg with 95% confidence limits of 58.5 – 78.3 mg/kg.

CLINICAL SIGNS *(TABLE 2 AND APPENDIX 1)*

Piloerection and hunched posture were observed in the animals of the various dose groups, starting 3-4 days (81 and 145 mg/kg groups) or 3-12 days (lower doses) after dosing. These changes were accompanied by hypoactivity in rats of the higher dose groups (81 and 145 mg/kg). Diarrhea was observed in two females of the 45mg/kg group 12-14 days after treatment.

Complete or partial recovery was achieved at the end of the observation period in the surviving animals.

BODY WEIGHT *(APPENDIX 2)*

Decrease in body weight or retarded growth was found in animals given the various doses during the observation period.

POST-MORTEM EXAMINATION

GROSS PATHOLOGY *(TABLE 3 AND APPENDIX 3)*

At the necropsy of animals which died before the end of the observation period, the main macroscopic findings were marked or moderate liver paleness and erosion and/or thinning walls of stomach. These changes were mainly confined to animals of the higher dose groups (81 and 145 mg/kg). Moreover, kidney medulla congestion and congestion of lungs or thymus were seen in a few animals.

At the autopsy carried out at the end of the observation period, no appreciable macroscopic findings were evident in any rat.

SUMMARY AND CONCLUSIONS

Experimental data from a toxicity study in which Sprague Dawley Crl:CD(SD) BR rats received oral administration of the test article [redacted] are given in this report.

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.1) and with Organization for Economic Cooperation and Development Guideline (section 4, subpart 401, Paris 1981 and subsequent revisions).

The test article was administered to the rats as a suspension in deionized water at the dosages of 45, 63, 81 and 145 to groups of 5 males/dose and at the dose of 45 mg/kg to 5 females for confirmation in the other sex. All rats were treated after a 16-hour fasting period. The day of treatment was considered day 1 of the study. The animals were weighed twice before treatment (at randomization and on day 1 just before treatment) and on days 3, 8 and 14 (surviving males in the 63 and 81 mg/kg groups and females in the 45 mg/kg group were also weighed on day 21). They were clinically observed for 14 or 21 days following the treatment. Macroscopic examinations were performed in the animals which died before the end of the study. At the end of the observation period the surviving rats were killed (fasted overnight) by excision of the femoral arteries after i.p. overdosage anesthesia with 5% sodium pentobarbital and were subjected to a thorough autopsy.

The mortality which occurred at the various doses is given below:

Dose (mg/kg)	45	63	81	145
Treated animals	5M+5F	5M	5M	5M
Mortality	0	2M	4M	5M
Total (%)	0%	40%	80%	100%

The deaths occurred 4-9 days after dosing, with the first case observed on day 4 after administration in the 145 mg/kg group.

No deaths occurred in the animals of either sex in the lowest dose group (45 mg/kg).

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The LD_{50} was calculated to be 67.7 mg/kg with 95% confidence limits of 58.5 – 78.3 mg/kg.

Piloerection and hunched posture were observed in the animals of the various dose groups, starting 3-4 days (81 and 145 mg/kg groups) or 3-12 days (lower doses) after dosing. These changes were accompanied by hypoactivity in rats of the higher dose groups (81 and 145 mg/kg). Diarrhea was observed in two females of the 45mg/kg group 12-14 days after treatment. Complete or partial recovery was achieved at the end of the observation period in the surviving animals. Moreover, decrease in body weight or retarded growth was found in animals given the various doses during the observation period.

At the necropsy of animals which died before the end of the observation period, the main macroscopic findings were marked or moderate liver paleness and erosion and/or thinning walls of stomach. These changes were mainly confined to animals of the higher dose groups (81 and 145 mg/kg). At the autopsy carried out at the end of the observation period, no appreciable macroscopic findings were evident in any rat.

In conclusion, the **LD_{50}** of the test article [redacted], when administered to rats by oral route, was **67.7 mg/kg (95% confidence limits: 58.5-78.3 mg/kg)**. The compound induced delayed toxicity (liver and stomach were mainly involved) in animals given the higher doses.

Dr. Ping Yu
Study Director
October 16, 1998

Dr. Sergio Peano
Senior Scientist for General Toxicology
Oct. 16, 1998

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GROUP DATA

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Test article: [redacted]

Title : Acute oral toxicity study in rats

RBM exp. : 980431

TABLE 1. - Mortality and LD50 calculation (p. 1)

Males - Females

Dose (mg/kg)		45	63	81	145
Treated animals		10	5	5	5
Day	4	0	0	0	1
	5	0	0	0	3
	6	0	0	0	1
	7	0	0	1	0
	8	0	2	2	0
	9	0	0	1	0
Total no.	(day 21)	0	2	4	5
Total (%)		0.0%	40.0%	80.0%	100.0%

Median lethal dose (LD50) = 67.72

95% confidence limits = 58.54 - 78.34

Slope (SE) = 5.15 1.58

Heterogeneity P = 0.963 NS

Linear regression y =-16.7295+5.1548x

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Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

TABLE 2. - Clinical signs (maximum daily frequency) (p. 1)
(no. of animals affected, from-to)

Males

Dose (mg/kg)	45	63	81	145
no. of treated animals	5	5	5	5
Death	-	2 8d	4 7d- 9d	5 4d- 6d
Hypoactivity	-	-	4 7d- 9d	4 4d- 5d
Piloerection	2 7d-12d	5 5d-18d	4 3d-16d	4 4d- 5d
Hunched posture	2 7d-12d	3 12d-16d	1 4d- 4d	4 4d- 5d
Recovery	5 13d	3 19d	1 17d	-

- (not observed) from-to (first-last observation in one or more animals)
Time : d (days)

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

TABLE 2. - Clinical signs (maximum daily frequency) (p. 2)
(no. of animals affected, from-to)

Females

Dose (mg/kg)	45
no. of treated animals	5
Piloerection	4 3d-16d
Hunched posture	2 12d-14d
Diarrhea	2 12d-14d
Recovery	5 17d

from-to (first-last observation in one or more animals)
Time : d (days)

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

TABLE 3. - Gross pathology examination (p. 1)
(no. of cases, mean severity, %)

Dead or agonal sacrificed an. Males

Dose (mg/kg)	45	63	81	145
no. of animals	0	2	4	5
no. of animals without appreciable lesions	0	1	0	0
General observation				
cannibalized	-	0	0	1 20.00%
Kidneys				
medulla, congestion	-	0	0	2(2.0) 40.00%
Liver				
pale	-	1(2.0) 50.00%	3(2.0) 75.00%	4(2.0) 80.00%
Lungs				
congestion	-	0	0	1(2.0) 20.00%

- (not examined)
Severity : 0(very slight) 1(slight) 2(moderate) 3(severe)

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

TABLE 3. - Gross pathology examination (p. 2)
(no. of cases, mean severity, %)

Dead or agonal sacrificed an. Males

Dose (mg/kg)	45	63	81	145
no. of animals	0	2	4	5
no. of animals without appreciable lesions	0	1	0	0
Stomach				
erosion	-	0	0	2(2.0) 40.00%
thinning walls	-	0	1(2.0) 25.00%	2(2.0) 40.00%
Thymus				
congestion	-	0	0	1(2.0) 20.00%

- (not examined)
Severity : 0(very slight) 1(slight) 2(moderate) 3(severe)

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

TABLE 3. - Gross pathology examination (p. 3)
(no. of cases, mean severity, %)

Final killing — Males

Dose (mg/kg)	45	63	81	145
no. of animals	5	3	1	0
no. of animals without appreciable lesions	5	3	1	0

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

TABLE 3. - Gross pathology examination (p. 4)
(no. of cases, mean severity, %)

Final killing	Females
Dose (mg/kg)	45
no. of animals	5
no. of animals without appreciable lesions	5

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APPENDICES

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 1. - Clinical signs incidence (p. 1)
(no. of animals affected)

Dose (mg/kg) 45

Cage # 7M	Day	1				2	3	4	5	6	7	8	9	10	11	12	13	14
	Time	30m	2h	4h	6h	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A
No clinical signs		5	5	5	5	5 5	5 5	5 5	5 5	5 5	3 3	3 3	3 3	3 3	3 3	3 3	5 5	5 5
Piloerection											2 2	2 2	2 2	2 2	2 2	2 2		
Hunched posture											1 1	2 2	2 2	2 2	2 2	2 2		

Cage # 8F	Day	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
	Time	30m	2h	4h	6h	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A	M A
No clinical signs		5	5	5	5	5 5	4 4	4 4	4 4	4 4	4 4	1 1	1 1	3 3	3 3	2 2	2 2	2 2	2 2	3 3	5 5
Piloerection							1 1	1 1	1 1	1 1	1 1	4 4	4 4	2 2	2 2	3 3	3 3	3 3	3 3	2 2	
Hunched posture																2 2	2 2	1 1			
Diarrhea																2 2	2 2	1 1			

Cage # 8F (follows)	Day	18	19	20	21
	Time	M A	M A	M A	M A
No clinical signs		5 5	5 5	5 5	5 5

Time: m (minutes) h (hours) M (morning) A (afternoon)

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Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 1. - Clinical signs incidence (p. 2)
(no. of animals affected)

Dose (mg/kg) 63

Cage # 11M	Day	1				2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17	
	Time	30m		2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
Death																			2																			
No clinical signs		5		5	5	5	5	5	5	5	5	5								1	1	1	1	1	1												
Piloerection													5	5	5	5	5	5	3	3	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3
Hunched posture																											3	3	3	3	3	3	3	3				

Cage # 11M (follows)	Day	18		19		20		21	
	Time	M	A	M	A	M	A	M	A
No clinical signs				3	3	3	3	3	3
Piloerection		3	3						

Time: m (minutes) h (hours) M (morning) A (afternoon)

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 1. - Clinical signs incidence (p. 3)
(no. of animals affected)

Dose (mg/kg) 81

Cage # 9M	Day	1				2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17	
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
Death																1		2		1																
No clinical signs		5	5	5	5	5	5	4	4	4	4	5	5	5	5																			1	1
Hypoactivity																4	4	2	2	1	1														
Piloerection								1	1	1	1					4	4	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Hunched posture										1	1																								

Cage # 9M (follows)	Day	18		19		20		21	
	Time	M	A	M	A	M	A	M	A
No clinical signs		1	1	1	1	1	1	1	1

Time: m (minutes) h (hours) M (morning) A (afternoon)

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 1. - Clinical signs incidence (p. 4)
(no. of animals affected)

Dose (mg/kg) 145

Cage # 5M	Day	1				2		3		4		5		6
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M
Death										1		3		1
No clinical signs		5	5	5	5	5	5	5	5					
Hypoactivity										4	4	1	1	
Piloerection										4	4	1	1	
Hunched posture										4	4	1	1	

Time: m (minutes) h (hours) M (morning) A (afternoon)

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Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 2. - Body weight (g) (p. 1)
(individual)

Dose (mg/kg) 45

Animal #		31M	32M	33M	34M	35M	36F	37F	38F	39F	40F
Week	day										
	0	297	242	269	285	281	230	219	222	223	207
1	1	271	222	245	265	257	217	207	208	210	194
1	3	288	218	269	277	278	224	221	190	221	196
2	8	290	211	278	278	279	187	208	161	230	167
2	14	318	223	311	290	299	179	210	160	240	160
3	21						200	233	197	269	190

REDACTED AS TO TRADE NAMES

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 2. - Body weight (g) (p. 2)
(individual)

Dose (mg/kg) 63

Animal #		51M	52M	53M	54M	55M
Week	day					
	0	300	268	257	278	287
1	1	284	254	232	248	267
1	3	306	276	258	285	289
2	8	238	210			250
2	14	191	172			193
3	21	256	249			276

REDACTED AS TO TRADE NAMES

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 2. - Body weight (g) (p. 3)
(individual)

Dose (mg/kg) 81

Animal #		41M	42M	43M	44M	45M
Week	day					
	0	299	270	300	302	267
1	1	280	250	278	279	244
1	3	271	258	285	283	247
2	8	220		224		
2	14	219				
3	21	254				

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 2. - Body weight (g) (p. 4)
(individual)

Dose (mg/kg) 145

Animal #		21M	22M	23M	24M	25M
Week	day					
	0	273	260	247	277	280
1	1	256	245	227	255	260
1	3	251	241	222	260	263

REDACTED AS TO TRADE NAMES

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 3. - Gross pathology examination (p. 1)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 63

An#	Death day/code#	TISSUE	Gross observations
53M	8 M2	General observation	no macroscopically appreciable lesions
54M	8 M2	Liver	pale, diffuse, moderate

Death code : M2(Natural death)

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 3. - Gross pathology examination (p. 2)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 81

An#	Death day/code#	TISSUE	Gross observations
42M	8 M2	Liver	pale, diffuse, moderate
43M	9 M2	Liver	pale, diffuse, moderate
44M	8 M2	Liver	pale, diffuse, moderate
		Stomach	thinning walls, diffuse, moderate

201

Death code : M2(Natural death)

REDACTED AS TO TRADE NAMES

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 3. - Gross pathology examination (p. 3)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 145

An#	Death day	code#	TISSUE	Gross observations
21M	5	M2	Kidneys	medulla, congestion, diffuse, moderate
			Liver	pale, diffuse, moderate
			Stomach	erosion, multifocal, moderate thinning walls, diffuse, moderate
22M	6	M2	Kidneys	medulla, congestion, diffuse, moderate
			Liver	pale, diffuse, moderate
			Thymus	congestion, diffuse, moderate
23M	5	M2	General observation	cannibalized
24M	5	M2	Liver	pale, diffuse, moderate
			Stomach	erosion, multifocal, moderate thinning walls, diffuse, moderate
25M	4	M2	Liver	pale, diffuse, moderate
			Lungs	congestion, diffuse, moderate

Death code : M2(Natural death)

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BIOSCIENCE LABORATORIES & CLINICS GROUP

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 3. - Gross pathology examination (p. 4)
(individual)

Final killing

Dose (mg/kg) 45

An#	Death day	T I S S U E	Gross observations
31M	15	General observation	no macroscopically appreciable lesions
32M	15	General observation	no macroscopically appreciable lesions
33M	15	General observation	no macroscopically appreciable lesions
34M	15	General observation	no macroscopically appreciable lesions
35M	15	General observation	no macroscopically appreciable lesions
36F	22	General observation	no macroscopically appreciable lesions
37F	22	General observation	no macroscopically appreciable lesions
38F	22	General observation	no macroscopically appreciable lesions
39F	22	General observation	no macroscopically appreciable lesions
40F	22	General observation	no macroscopically appreciable lesions

102

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 3. - Gross pathology examination (p. 5)
(individual)

Final killing

Dose (mg/kg) 63

An#	Death day	T I S S U E	Gross observations
51M	22	General observation	no macroscopically appreciable lesions
52M	22	General observation	no macroscopically appreciable lesions
55M	22	General observation	no macroscopically appreciable lesions

103

Test article: [redacted]
Title : Acute oral toxicity study in rats
RBM exp. : 980431

APPENDIX 3. - Gross pathology examination (p. 6)
(individual)

Final killing

Dose (mg/kg) 81

An#	Death day	T I S S U E	Gross observations
41M	22	General observation	no macroscopically appreciable lesions

101